Biotinidase Deficiency

Primary Defect

Deficiency of the enzyme affects normal biotin (one of the B vitamins) recycling. This results in a biotin deficiency.

Screening Test

Colorimetric assay of enzyme activity.

Etiology & Prevalence

Genetic (autosomal recessive)

Occurs in about 1 in 87,000 births

If Untreated

Severe deficiency may result in metabolic crisis, coma and death
Neurological impacts include convulsions, developmental delay, hearing loss, visual impairment.
Other effects include skin rash and hair loss.

Therapy

Oral biotin replacement

With Treatment

Treatment before onset can prevent all symptoms. Treatment after onset will resolve some symptoms but will not reverse all damage.

Cystic Fibrosis (CF)

Primary Defect

A defective protein disrupts the movement of salt and water across cell membranes. A primary effect of this is accumulation of thick mucus that interferes with lung and digestive function.

Screening Test

Immunoassay to measure the pancreatic enzyme immunoreactive trypsin (IRT) followed by DNA analysis for those with elevated levels. 3% to 5% false negative rate. Positive predictive value is nearly 100% when two defective genes are found, 5-10% when only a single defective gene is found (based on data from Wisconsin with DNA testing for the common mutation only).

Etiology & Prevalence

Genetic autosomal recessive. A single mutation (delta F508) is most common in Northern Europeans and is associated with severe clinical outcomes. However, hundreds of other mutations have been identified, some with more mild disease states. There is significant clinical variability, however, even among those with identical genetic defects.

Occurrence (and genotype) is highly variable among different populations. About 1 in 2000 Northern European, 1 in 17,000 African American and 1 in 9,000 Hispanic infants are affected.

If Untreated

Substantial impact on lung function, increased lung infections, and malnutrition due to abnormal production of pancreatic enzymes. Other features include cirrhosis of the liver, abnormal glucose tolerance, and infertility.

Therapy

Currently only palliative therapies are available. These are aimed primarily at maintaining lung function, preventing infection, and enhancing nutritional status.

With Treatment

Improved treatments have dramatically increased life expectancy for affected individuals from approximately 3 years in the 1950's to the late 30's today. The impact of early detection through newborn screening is not fully understood, however. Improved nutritional status in early childhood has been shown, but the long-term benefits remain to be determined.

Galactosemia

Primary Defect

Deficiency in enzymes that help convert galactose into glucose. The body cannot use galactose directly.

Screening Test

Fluorescent assay for enzyme activity
Typically followed by measurement of galactose if reduced activity is detected

Etiology & Prevalence

Genetic (autosomal recessive)
Occurs in about 1 in 50,000 births

If Untreated

Jaundice, vomiting, lethargy, hepatosplenomegaly, cataracts and failure to thrive leading to liver failure, sepsis. Often fatal

Therapy

Galactose free diet for life with strict avoidance of lactose (milk sugar) and lactose containing foods.

With Treatment

Mortality avoided if detected in time; improved IQ if treated early but typically in the low end of normal; speech and learning disabilities are common; ovarian failure for most females.

Glucose-6-Phosphate Dehydrogenase Deficiency (G-6-PD deficiency)

Primary Defect

Defect in the structure of the G-6-PD enzyme, which plays a role in protecting hemoglobin from oxidative damage leading to hemolysis.

Screening Test

Fluorescent spot test that measures G-6-PD enzyme activity.

Etiology & Prevalence

Genetic – X linked recessive, several hundred mutations have been described.

A defective gene is found in 1 in 50 Southeast Asians, 1 in 10 Mediterraneans (Italian, Greek, Middle Eastern) and 1 in 10 African Americans, less than 1 in 1,000 northern Europeans. The degree of enzyme deficiency is related to mutation involved and gender.

If Untreated

Varies depending on residual enzyme activity. Most persons with deficiency never suffer any clinical manifestations. Mediterranean and Asian forms have greater deficiency with neonatal jaundice, and episodic hemolytic anemia prominent features. The African American form is less severe due to residual enzyme activity, although hemolytic anemia may occur. Hemolysis may be triggered by exposure to oxidant drugs or infections. Consumption of Fava beans can induce hemolysis in some with the Mediterranean forms.

Therapy

Phototherapy for neonatal jaundice. Avoidance of oxidant drugs such as antimalarials and sulphonamides, and avoidance of fava beans for those with the Mediterranean forms. Transfusion may be used to counteract severe episodes of jaundice or hemolysis.

With Treatment

Resolution of jaundice in the newborn. Reduced incidence of hemolytic episodes.

Early Hearing Loss

Primary Defect

Hearing loss, present at birth, may be unilateral or bilateral, and range from mild (hard of hearing) to profound (deaf).

Screening Test

Two types of electrophysiologic procedures are used to screen newborns: auditory brainstem response testing (ABR) and otoacoustic emission testing (OAE).

Etiology & Prevalence

Genetic (syndromic or nonsyndromic), or Environmental
Occurs in about 3 in 1,000 births, (Washington State 80-239 births/yr)
Most frequently occurring birth defect

If Untreated

Hearing loss interferes with the ability to communicate with others.
It negatively impacts speech and language acquisition, academic achievement, social and emotional development, resulting in lower educational and employment levels in adulthood.

Therapy

Auditory-Verbal Approach: Once the child has appropriate amplification (hearing aids or cochlear implants), child is taught to listen in a natural environment.
Bilingual-Bicultural Approach: American Sign Language is used and English is taught as a second language through reading and writing. Emphasis on the deaf culture.
Cued Speech: Hand shapes and lip reading are used to communicate.
Oral Approach: Requires child to use spoken language and face-to-face communication, once the child has appropriate amplification devices.
Total Communication: Combination option using any of the above methods of communication.

With Treatment

Improved speech and language skills, school achievement, self-esteem, and psychosocial adaptation.
Children who receive intervention by six months of age maintain language development commensurate with their cognitive abilities through the age of 5 years.

Homocystinuria

Primary Defect

Deficiency or absence of an enzyme necessary for the breakdown of the amino acid methionine results in build up of methionine in the blood and elevated excretion of homocystine in the urine.

Screening Test

Historically screening has been based on measurement of methionine in the dried blood spot using a bacterial inhibition assay similar to the original Guthrie assay for PKU. Screening is now possible using tandem mass spectrometry (MS/MS). Predictive value should be high. Because of delayed accumulation of methionine if residual enzyme activity is present, screening may be more effective at 2 to 4 weeks of age for these infants.

Etiology & Prevalence

Genetic, autosomal recessive. A number of specific genetic defects have been identified. With some, residual enzyme activity may occur, resulting in moderation of symptoms and delay in accumulation of elevated levels of methionine.

Prevalence estimates vary between 1 in 80,000 to 1 in 500,000. Possibly due to variation in sensitivity of the screening tests with age.

If Untreated

There is wide variation in clinical course for affected infants. Clinical features include: circulatory blood clotting (thromoembolism), physical and mental developmental disabilities. Approximately half die by age 25 due to thromboembolism. Developmental delay and physical defects affect most. The most common defect (cystathionine β-synthase deficiency) can be classified as either responsive or non-responsive to treatment with vitamin B6. This may be related to residual enzyme activity needed for response. Those who are not responsive have more severe clinical course.

Therapy

Vitamin B6 supplementation for those who are responsive. Dietary restriction of methionine with supplementation of cystine for those who are not. Other treatment focused on clinical features such as aspirin to combat thromboemblism.

With Treatment

Mortality and mental retardation are prevented or reduced. Clinical variability of other features remains.

Medium Chain Acyl-coA Dehydrogenase Deficiency (MCADD)

Primary Defect

Defect in production of MCAD enzyme which functions in metabolizing fatty acids.

Screening Test

Tandem mass spectrometry to measure octanoylcarnitine, a product of fatty acid metabolism that accumulates if the MCAD enzyme is deficient.

Etiology & Prevalence

Genetic (autosomal recessive)

1 in 10,000 to 1 in 25,000 (data from United Kingdom)

If Untreated

Variable expression, however, fasting or infection can trigger acute episodes of hypoglycemia leading to rapid crisis or death (30% mortality following first episode). Up to 5% of deaths attributed to Sudden Infant Death Syndrome may in fact be caused by undiagnosed MCAD deficiency.

Therapy

Avoidance of fasting with special care during illness, reduction of dietary fat.

With Treatment

Crisis episodes avoided, no apparent consequences.

Maple Syrup Urine Disease (MSUD)

Primary Defect

Deficiency or absence of an enzyme needed to break down the branched chain amino acids, leucine, isoleucine, and valine. This results in increased serum levels of these amino acids and ketoacid intermediates.

Screening Test

Historically screening has been based on measurement of leucine in the dried blood spot using a bacterial inhibition assay similar to the original Guthrie assay for PKU. Screening is now possible using tandem mass spectrometry to measure the amino acids. Predictive values are not documented but should be high.

Etiology & Prevalence

Genetic, autosomal recessive. A number of specific genetic defects have been identified. With some, residual enzyme activity may occur, resulting in moderation of symptoms.

About 1 in 130,000 infants expected in Washington State. It occurs in about 1 in 760 births to Mennonite families.

If Untreated

Lethal for the classical form (absent enzyme activity), usually in the first month of life. If residual enzyme activity is present, children develop mental and physical retardation.

Therapy

Dietary restriction of branched chain amino acids. Requires specialized medical and nutritional intervention.

With Treatment

Variable. Outcome is related to age and neurological symptoms at the time therapy is initiated. Treated infants may have retardation related to onset of symptoms before screening test results are communicated. Highly coordinated screening system is essential since irreversible damage or death can occur within the first two weeks of life.

Congenital Toxoplasmosis

Primary Defect

Congenital infection by the protozoan *Toxoplasmosis gondii* (a parasite associated with cats and raw or undercooked meat)

Screening Test

Enzyme linked immunosorbent assay (ELISA) test of blood dried on filter paper for Ig-M antibodies to *T. gondii*

Etiology & Prevalence

Infectious disease - Infection of fetus can occur if mother acquires infection during pregnancy (infection is transmitted across that placenta or, occasionally, during birth). Infections acquired early in pregnancy have more severe impact than those acquired late, however, those acquired late are more common.

Occurs in about 1 in 10,000 births

If Untreated

Mental retardation, neurological impairment, severe visual impairment, some mortality (frequency is uncertain).

Therapy

Twelve to twenty four month course of treatment with combinations of antibiotics, notably pyrimethamine, sulfadiazine, spiramycin. Additional treatment may be needed to counteract toxicity of pyrimethamine.

With Treatment

May stop acute infection and reduce damage to organs. Outcome appears to be improved but magnitude is not yet fully determined. Data from available studies is limited and the impact on long-term outcome is unclear.